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Neurons in the Primate Orbitofrontal Cortex Respond to Fat Texture Independently of Viscosity

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Verhagen, Justus V., Edmund T. Rolls, and Mikiko Kadohisa. Neurons in the primate orbitofrontal cortex respond to fat texture independently of viscosity. *J Neurophysiol* 90: 1514–1525, 2003. First published May 21, 2003; 10.1152/jn.00320.2003. The primate orbitofrontal cortex (OFC) is a site of convergence from primary taste, olfactory, and somatosensory cortical areas. We describe the responses of a population of single neurons in the OFC that respond to orally applied fat (e.g., safflower oil) and to substances with a similar texture but different chemical composition, such as mineral oil (hydrocarbon) and silicone oil [$(Si(CH_3)_2O)_n$]. These findings provide evidence that the neurons respond to the oral texture of fat, sensed by the somatosensory system. Use of an oral viscosity stimulus consisting of carboxymethyl-cellulose in the range 1–10,000 centipoise (cP) showed that the responses of these fat-sensitive neurons are not related to stimulus viscosity. Thus a textural component independent of viscosity and related to the slick or oily property is being used to activate these oral fat-sensitive neurons. Moreover, a separate population of neurons responds to viscosity (produced, e.g., by the carboxymethyl-cellulose series), but not to fat with the same viscosity. Thus there is a dissociation between texture channels used to sense fat viscosity and non–fat-produced viscosity. Further, free fatty acids such as linoleic acid do not activate these neurons, providing further evidence that the oral fat-sensing mechanism through which these OFC neurons are activated is not gustatory but textural. Most of this population of fat-sensitive neurons receive convergent taste inputs. These results provide evidence about how oral fat is sensed and are relevant to understanding the physiological and pathophysiological processes related to fat intake.

INTRODUCTION

Fat is an important component of normal food intake in primates and it is palatable. Humans are natural omnivores, who, like macaques, have evolved to consume a diet (after weaning) that consists of vegetable matter supplemented by protein-rich and fat-rich food sources that are a valuable source of essential amino acids and fats. Essential fatty acids include the n-6 (including linoleic acid and its derivative, arachidonic acid) and n-3 fatty acids (including α-linolenic acid and its derivative docosahexaenoic acid; Connor et al. 1992). Dietary essential fatty acid deficiency in primates results in reduced learning, impaired vision and polydipsia (n-3 deficiency), and growth retardation, skin lesions, reproductive failure, fatty liver, and polydipsia (n-6 deficiency; Connor et al. 1992).

Mechanisms that sense and regulate the dietary intake of fat are of great importance clinically. In particular, high dietary fat intake is strongly implicated in the etiology of cardiovascular morbidity and deaths (Keys 1970). Studies of satiety in normal human subjects indicate that high fat foods may not produce satiety or reduce hunger ratings to the same degree as isocaloric high carbohydrate or high protein–containing foods, and that foods containing fat may be overeaten in terms of and because of their high energy density (Bell et al. 1998; Warwick et al. 1993). Together these data indicate that fat in the diet may help to make food palatable and that, because of its energy density, it may be important to actively monitor fat intake. The research described in this study investigates the mechanisms that sense oral fat and the neural representation of oral fat.

We use the term "fat" to refer to natural triglycerides, molecules consisting of one glycerol esterified to three fatty acids. Triglycerides are of special importance because natural oils consist almost entirely of triglycerides, and have little free fatty acids (ffa). Three main classes of ffa exist, based on the number of double bonds: saturated (e.g., lauric and stearic acid), monounsaturated (e.g., oleic acid), and polyunsaturated fatty acids (e.g., linoleic acid) (Weiss 1983).

The perception of fats and ffas may be dependent on a combination of modalities: textural, olfactory, nociceptive, thermal, and gustatory, as shown next. Gustatory mechanisms have been revealed in rat oral taste cells that may mediate a possible fat taste: the slow modulation of K-channels by polyunsaturated ffa such as linoleic acid (Gilbertson 1998; Gilbertson et al. 1997) and the presence of a fat transporter (Fukuwatari et al. 1997). However, salivary lipase, which could release fatty acid from fat in rats to activate such a mechanism, is hardly present in humans (Gilbertson 1998), so that this mechanism may not be important in humans. Further evidence that this chemical-sensing mechanism may not be important in primates, including humans, is that the time course of the activation of the K-channel mechanism is very slow (Gilbertson 1998) and does not match the rapidly developing subjective sensation of fat in the mouth (personal observations E. T. Rolls and J. V. Verhagen); and that primate orbitofrontal cortex (OFC) neurons that respond to fat in the mouth use a texture rather than a taste information channel (Rolls et al. 1999). Fatty acids below C10 may taste sour (e.g., formic and propionic acid; Forss 1972) but are not recognized as fatty. High boiling point lipids are tasteless, probably because of their low water solubility (Forss 1972). Thermal cooling might contribute to the sensations produced by the melting of several fats, e.g., butter and chocolate (Forss 1972; Litman and Numrych 1978).

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Nociceptive input produced by ffas was previously described by Bryant and Moore (1995); ffas (and also carbon dioxide) may stimulate cold nociceptors and lingual trigeminal activity. Lingual trigeminal fibers are stimulated more as the lipophilicity of the straight-chain fatty acid increases (C1–C6). Blocking epithelial junctions with $LaCl_3$ does not affect the fibers' responsiveness to the fatty acid, suggesting that fas reach the free nerve endings by diffusing through the lipid epithelial transcellular pathway.

Many ffas and their derivatives are volatile and flavorful and are frequently used to create artificial flavors (Litman and Numrych 1978). Glycerides on the other hand are not volatile but can act as reservoirs of volatile flavor. Lipids can contribute both positively and negatively to the flavor of a food. For example, the flavor of blue-mold cheese depends almost entirely on the presence of ffa, methyl ketones, and methyl carbinols derived from lipolysis of milk fat (Litman and Numrych 1978). The principal flavorant of mushroom is 1-octen-3-ol, which is derived from linoleic acid. Thermal and oxidative decompositions of triglycerides in deep-fat frying oils cause the formation of volatile compounds contributing to deep-fried flavor. Finally, the fatty acid content in the serum of milk determines the degree of rancid flavor and acceptability (Litman and Numrych 1978).

The texture felt in the mouth during tongue movements, chewing, and swallowing is also important for the perception of fat. Several oral textural qualities depend on the fat content of a food and include creamy, juicy, greasy, viscous, and smooth (Cooper 1987; Drewnowski 1987).

In previous investigations of the neural bases of taste, olfaction, and feeding in primates (see Rolls 1995, 1997, 1999, Rolls and Scott 2003), it has been shown that the primate OFC contains the secondary taste cortex (Baylis et al. 1994) and that taste neurons that are found in it (Rolls et al. 1990) respond to the taste of food only when the monkey is hungry (Rolls et al. 1989). There are also projections from the primary olfactory cortex to the orbitofrontal cortex (Carmichael et al. 1994), and the responses of neurons in this secondary and tertiary olfactory cortex represent the reward value of the odor of food, in that the neurons here show olfactory sensory-specific satiety (Critchley and Rolls 1996a; Rolls and Rolls 1997). The flavor of food is represented, and is probably formed, in this region given that, in addition to unimodal taste and olfactory neurons in this region, other single neurons respond to both taste and olfactory stimuli (Rolls and Baylis 1994) and learn olfactory-to-taste associations (Rolls et al. 1996). In addition to these inputs, there is a somatosensory input to the OFC from the somatosensory cortex (Carmichael and Price 1995), and neurons that respond to what is probably in part a somatosensory stimulus, tannic acid, are found in the OFC (Critchley and Rolls 1996b).

Rolls et al. (1999) discovered a neuronal representation in the macaque OFC of fat in the mouth and showed that the sensing mechanism is based on the texture (somatosensory) and not the chemical (gustatory) properties of the fat, in that the same neurons are activated by nonfat compounds with a similar slick texture such as silicone oil and mineral oil (pure hydrocarbon). These neurons are described as fat-sensitive because they respond to the fats found in food. Rolls et al. (1999) also showed that some of these neurons show multimodal convergence because they can also be activated by taste and/or by olfactory stimuli.

Here we describe analyses of the inputs to orbitofrontal oral fat-sensitive neurons. First, we tested whether their responses to fat depend on just the viscosity of the texture in the mouth, or whether the responses to fats are independent of viscosity. We investigated this by measuring the responses of the neurons to a set of viscosity stimuli made from carboxymethylcellulose (CMC), which is odorless and tasteless, made up in a water base. The viscosity series was log-unit spaced in the range 1 to 10^4 centipoise (cP). The responses of the neurons were also measured to a set of fats and oils with measured viscosity, so that we could determine whether the responses to the fats and oils were based on viscosity. Second, to test whether these OFC fat-sensitive neurons respond to fat based on gustatory effects produced by any unsaturated ffa that may be present (Gilbertson 1998), we tested whether these neurons respond to aqueous solutions of linoleic acid (polyunsaturated) and lauric acid (saturated, and therefore, used as according to Gilbertson's hypothesis, it should be ineffective), as well as the natural oils rich in their triglycerides (safflower and coconut oil, respectively). To provide further evidence on whether these neurons respond to the texture that is typical of fat rather than by chemical sensing, and to exclude any possible olfactory effect being produced by any of the stimuli, we included low-odor silicone oil and mineral oil (pure hydrocarbon) of measured viscosity in the set of stimuli.

METHODS

Subjects

The recordings were made in three hemispheres of two rhesus macaques (*Macaca mulatta*; one female weighing 2.6–3.3 kg and one male weighing 5.1–5.6 kg). The monkeys were pair housed in foraging home cages. To ensure that the macaques were willing to ingest the test foods and fluids during the recording sessions, they were on mild food (150 g of nutritionally balanced mash plus fruits, boiled chicken eggs, nuts, and seeds) and fluid (1 h/day ad libitum water) deprivation, in that both were provided after the daily recording session. The monkeys showed steady increases in body weight. All procedures, including preparative and subsequent ones, were carried out in accordance with the "Policy on the use of animals in neuroscience research" of the Society for Neuroscience, and were licensed under the U.K. Animals (Scientific Procedures) Act 1986.

Recordings

Recordings were made from single neurons in the OFC, which included both the medial and lateral areas in which taste and olfactory responses were previously described (see Rolls 1997; Rolls and Baylis 1994), using neurophysiological methods as described previously (Rolls et al. 1990; Scott et al. 1986a,b). The recordings were made with epoxylite-coated single-neuron tungsten microelectrodes (Frederic Haer, St. Bowdoinham, ME; unzapped, 5–10 MΩ at 1 kHz). After several tracks, when the impedance had fallen below 2 MΩ, we recoated the electrodes with epoxylite (6001M, Epoxylite, Bradford, UK), resulting in 5–10 MΩ impedance and good isolation (Verhagen et al. 2003). The signal-to-noise ratio was typically 3:1 or higher.

For on-line monitoring of neural activity and for determining the randomized permutation stimulus sequence during an experiment, a computer (Pentium) with real-time digital and analog data acquisition collected spike arrival times and displayed a peristimulus time histogram and rastergrams, and displayed the number of spikes in 1- and

3-s poststimulus periods. The spikes for this system were derived from an oscilloscope Schmitt trigger set to trigger on spikes in the signal from the microelectrode after amplification and band-pass filtering (500–5,000 Hz). To ensure that the recordings were made from single cells, the interspike interval was continuously monitored to make sure that intervals of <2 ms were not seen, and the waveform of the recorded action potentials was continuously monitored. The data were also collected using a Datawave Discovery (Tucson, AZ) system, which digitized the signal (12 bit, 16 kHz) for 8 s after stimulus onset. The spikes were sorted off-line using the cluster-cutting method provided with the Datawave system, and this procedure was straightforward as the data were collected with single-neuron microelectrodes that typically recorded from only one neuron at a time with a high signal-to-noise ratio. The recording sessions lasted 4 to 6 h and were conducted daily. To prevent visual associative input from evoking neural activity, we prevented the monkeys from seeing the stimuli by a view-obstructing screen. For further details see Rolls et al. (1990). No more than two complete experiments, on different neurons, were performed per day to limit the effects of satiety on neural responses. (The total application volume was 70 ml for the full stimulus set including rinses.)

Localization of recordings

X-radiography was used to determine the position of the microelectrode after each recording track relative to permanent reference electrodes and to the anterior sphenoidal process. This is a bony landmark whose position is relatively invariant with respect to deep brain structures (Aggleton and Passingham 1981). Microlesions (100 μA anodal, 100 s) made through the tip of the recording electrode during the final tracks were used to mark the location of typical units. These microlesions together with the associated X-radiographs allowed the position of all cells to be reconstructed in the 50-μm brain sections with the methods described by Feigenbaum and Rolls (1991).

Stimuli

Orbitofrontal cortex neurons were tested for their responsiveness to the set of taste, viscosity, and oily stimuli at room temperature (23°C), as shown in Table 1. The gustatory stimuli used included 1.0 M glucose (G), 0.1 M NaCl (N), 0.01 M HCl (H), 0.001 M QuinineHCl (Q), and 0.1 M monosodium glutamate (M). The concentrations of most of the tastants were chosen because of their comparability with our previous studies, and because they are in a sensitive part of the dose–response curve. The control stimulus was distilled water, termed V1 because it has a viscosity of 1 cP and is part of the viscosity series. For an additional comparison, the neuronal responses were tested to 20% black currant juice (BJ, Ribena) because with its complex taste and olfactory components and high palatability it is an effective stimulus when searching for and analyzing the responses of cortical neurons (Rolls et al. 1990).

To test for and analyze the effects of oral fat on neuronal activity, a set of oils and fat-related stimuli was included. The triglyceride-based oils consisted of vegetable oil, safflower oil, and coconut oil. These were used to examine whether fat is represented in the responses of cortical (taste) neurons. Single cream (SC, 18% fat, viscosity: 12 cP, Coop brand, pasteurized) was used as an exemplar of a natural high fat–content food of the type for which we sought to examine the neural representation and sensing mechanisms. All the neurons with fat-related responses described in this and our earlier study (Rolls et al. 1999) responded well to single cream. The monkeys had been raised on their mother's milk, which is a good source of dietary fat. Vegetable oil (VO, 59.5% monounsaturates, 34% polyunsaturates, and 6.5% saturates, viscosity 55 cP at 23°C) was used as a natural high-fat stimulus.

Because Gilbertson and colleagues (1997) reported differential effects in isolated taste cells to linoleic and lauric acid in vitro, suggesting that the gustatory modality might be involved in orally sensing fat, we included in the stimulus set free linoleic (LiA, 100 μM) and lauric acid (LaA, 100 μM) sodium salts (Sigma**)**, as well as oils rich in conjugated linoleic acid (safflower oil, SaO, 68–83%, 50 cP; Aldrich) and lauric acid (coconut oil, CO, 45–50%, 40 cP, melting point 26°C; Sigma) (Weiss 1983; Wills et al. 1998). The fatty acid–containing substances were all stored in the dark at 4°C under nitrogen, with further precautions taken to avoid any oxidation before use, and they were dissolved in N_2-purged distilled water (containing 5 mM NaCl standard).

To investigate whether the neurons responsive to fatty acid–based oils were in some way responding to the somatosensory sensations elicited by the fat, stimuli with a similar mouth feel but nonfat chemical composition were used. These stimuli included paraffin/mineral oil (pure hydrocarbon, viscosity 25 cP at 23°C; Sigma) and

TABLE 1. *Stimuli*

Stimulus	Abbreviation	Concentration	MW	Approximate Viscosity (cP)	Chemical Group
Glucose	G	1 M	180	1	Monosaccharide aldohexose
Black currant juice	BJ	20%		1	Mixture
Monosodium glutamate	M	0.1 M	187	1	Amino acid salt
NaCl	N	0.1 M	58	1	Inorganic salt
HCl	H	0.01 M	36	1	Inorganic acid
Quinine HCl	Q	0.001 M	387	1	Alkaloid
Water	V1 or 1 cP	5 mM NaCl		1	
CMC	V10 or 10 cP	0.2 g + 1l V1	700,000	10	Polysaccharide
CMC	V100 or 100 cP	4.0 g + 1l V1	700,000	100	Polysaccharide
CMC	V1000 or 1000 cP	11.0 g + 1l V1	700,000	1000	Polysaccharide
CMC	V10000 or 10000 cP	24.0 g + 1l V1	700,000	10,000	Polysaccharide
Mineral oil	MO	100%		25	Hydrocarbon mixture
Silicone oil	SiO or SilO	100%		100 or 280	Silicon–oxygen polymer
Vegetable oil	VO	100%		55	Fat
Coconut oil	CO	100%		40	Fat
Safflower oil	SaO or SafO	100%		50	Fat
Single cream	SC	100%		12	Emulsion
Lauric acid	LaA	100 μM		1	ffa
Linoleic acid	LiA	100 μM		1	ffa

silicone oil [$(Si(CH_3)_2O)_n$, SiO, 98 cP (Brookfield viscometer calibration fluid) or 280 cP (Aldrich)].

A viscosity series was made with CMC (high viscosity, MW 700,000; Sigma), a virtually odorless and tasteless thickening agent used widely in the food industry. Based on psychophysical data from Theunissen and Kroeze (1995), a log–linear relationship exists between the rated oral thickness of CMC and its apparent viscosity. (The term "apparent viscosity" is used to indicate that the CMC solutions do not behave rheologically as Newtonian fluids: they show shear-thinning behavior.) Viscosity was assessed using a calibrated Brookfield rotary viscometer (type LVT, Brookfield Engineering Laboratories, Middleboro, MA) at 60 rpm (shear rate about 12 s^{-1}) at 23°C. Concentrations (in g CMC added to 500 ml water) yielding 1, 10, 100, 1,000, and 10,000 cP (V1, V10, V100, V1000, and V10000, respectively; reliability ±10%) solutions were 0.0, 0.1, 2.0, 5.5, and 12.0 g CMC, respectively (values similar to those of Theunissen and Kroeze 1995). The solutions were mixed until they were optically clear. Viscosity was assessed at room temperature after air bubbles had disappeared. [To provide the reader with insight into these viscosity values, the viscosity of water is 1 cP; of vegetable oil, 55 cP (see Table 1); and of glycerol, 1759 cP (all at about 20°C).]

The stimuli were kept in the dark at −20°C for up to 1 mo. After thawing they were used for up to 5 days stored overnight at 4°C in the dark.

Stimulus delivery

The general method for stimulus delivery and accurate stimulus onset marking (Rolls et al. 1990) was modified (by J.V.V.) by introducing repeater pipettes. We used repeater pipettes (Eppendorf AG, Hamburg, Germany, type Multipette Plus) and pipette tips (Combitips Plus, 10 ml), which were modified by insertion of a stainless steel wire (0.5 mm diameter) into the lumen 10 mm from the tip. The wire was tightly coiled about 10 times around the tip extending toward the neck and glued at the neck with epoxy glue. For stimulus delivery, the pipette tip (and thus the wire that encircled it and was connected electrically to the fluid inside the pipette) was placed on antistatic conducting foam, which was in turn connected to an impedance-sensitive device that could send a Schmitt-triggered pulse to the data acquisition system. When fluid was expelled from the pipette and touched the tongue, the impedance to ground changed, and the pulse was triggered. We placed 10-mm-long cones cut from 200-μl Gilson pipette tips onto the tip of the repeater pipette tip, creating a fluid-free lumen, to prevent the system from being triggered when the tip touched the monkey's lips. For reliable triggering, a concentration of 5 mM NaCl was used to make the solution sufficiently conductive for the impedance system to trigger. [This concentration is well below the salivary NaCl + KCl concentration of about 25–30 mM (Bartoshuk 1974; Guinard et al. 1998; Morino and Langford 1978; Nagler and Nagler 2001).] All water-soluble stimuli were thus made up to contain 5 mM NaCl. Oil stimuli were triggered manually by touching the antistatic foam at the time of expelling the fluid from the tip. The tips were wiped clean before each stimulus presentation. To allow for consistent flow patterns, air bubbles in the pipette were removed and the pipette tips were cut back to an opening diameter of 1.5 mm. For chronic recording in monkeys, a manual method for stimulus delivery was used because it allows for repeated stimulation of a large receptive surface despite different mouth and tongue positions adopted by the monkeys (Scott et al. 1986a,b). The stimulus application volume was 200 ± 10 μl because this is sufficient to produce large gustatory neuronal responses that are consistent from trial to trial, and yet do not result in large volumes of fluid being ingested that might, by producing satiety, influence the neuronal responses (Rolls et al. 1989, 1990).

The monkey's mouth was rinsed with 200 μl V1 (water) during the intertrial interval (which lasted ≥30 s, or until neuronal activity returned to baseline levels) between taste stimuli. The complete stimulus array was delivered in random sequence. Because of the tenacious nature of the oral coating resulting from the delivery of cream or of oil, four 200-μl rinses with V1 were given, while allowing the subjects to swallow after each rinse. For V1000 and V10000, we used two such rinses. All the stimuli shown in Table 1 were delivered in permuted sequences, with the computer specifying the next stimulus to be used by the experimenter. The spontaneous firing rate of the neuron was estimated from trials in which no stimulus delivery occurred.

Data analysis

After cluster cutting of the spikes with Datawave software, the numbers of spikes of the single neuron in eighty 100-ms time bins starting at the onset of the stimulus were obtained using Microsoft Excel 9.0. Statistical analysis was performed on the numbers of spikes in the first 1-s period after stimulus onset, which was sufficiently long to include firing to even viscous liquids, and sufficiently short so that low viscosity taste stimuli were still activating the neurons, as shown in Fig. 1. An ANOVA was performed (with SPSS, Chicago, IL) to determine whether the neuron had significantly different responses to the set of stimuli and, if so, post hoc LSD *t*-tests were performed to test for significant differences between individual stimuli. If the main ANOVA was significant, two further ANOVAs were performed to test for differences in neuronal responses between the set of taste stimuli (G, N, H, Q, M, and V1) and between the members of the viscosity series V1–V10000. Systat 10 was used for the generation of Pearson product-moment correlation coefficients calculated between the stimuli using the responses of all the neurons analyzed, and graphical presentation of stimulus similarity using multidimensional scaling (loss function: Kruskal; regression: mono) and cluster analysis (linkage: average, distance: Pearson).

A taste cell was defined by a significant effect in the ANOVA performed across the stimulus subset (V1, G, N, M, H, Q) on the number of spikes during the first second after stimulus onset. Similarly, the viscosity cell criterion was based on a significant effect in the ANOVA between the set of stimuli V1–V10000. Fat cells were defined by a significant difference between the pooled response rates evoked by the oils (viscosity 25–100 cP, excluding mineral oil when its viscosity was 280 cP instead of 100 cP: 50% of the cells recorded, all from the female monkey) and the pooled rates of V10 and V100; and additionally by a significant difference between the pooled rates evoked by the oils and the spontaneous activity. The critical alpha level was set at $P < 0.05$ (although for most cells, 51/56, the P value in the overall ANOVA was <0.001).

The breadth-of-tuning metric of Smith and Travers (1979) was calculated as follows. The proportion of a neuron's total response that is devoted to each of the four basic stimuli can be used to calculate its coefficient of entropy (H). The measure of entropy is derived from information theory, and is calculated as

$$H = -k\Sigma_i p_i \log p_i$$

where H is the breadth of responsiveness, k is the scaling constant (set so that $H = 1.0$ when the neuron responds equally well to all stimuli in the set of size n), and p_i is the response to stimulus i expressed as a proportion of the total response to all the n stimuli in the set. The coefficient ranges from 0.0, representing total specificity to one of the stimuli, to 1.0, which indicates an equal response to all of the stimuli. The sparseness of the representation a can be measured (Rolls and Deco 2002; Rolls and Tovee 1995; Rolls and Treves 1998), by extending the binary notion of the proportion of neurons that are firing, as

$$a = \left(\sum_{i=1,N} r_i/N \right)^2 \Big/ \sum_{i=1,N} (r_i^2/N)$$

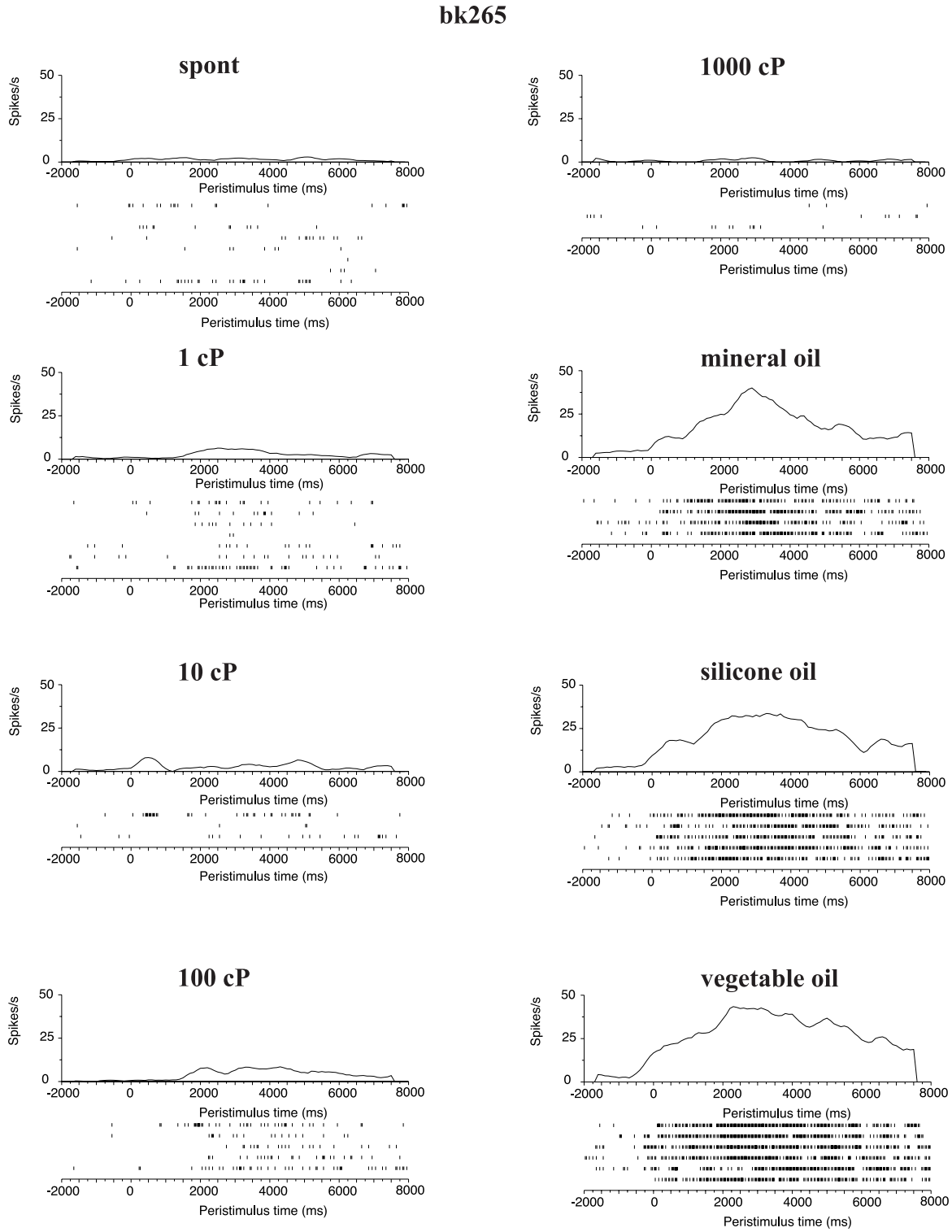

FIG. 1. Poststimulus-time histogram and rastergram of fat-responsive neuron (bk265). This neuron did not respond to CMC (carboxymethylcellulose) viscosity series (labeled 1–1000 cP) but did respond strongly to oils.

where r_i is the firing rate of the ith neuron in the set of N neurons. The sparseness is within the range 0–1, and assumes the value 0.5 for a fully distributed representation with binary encoding; and $1/N$ for a local or grandmother cell representation with binary encoding. These measures of the fineness of the tuning of neurons are important in understanding the neuronal encoding of information (Rolls and Deco 2002; Rolls and Treves 1998).

Screening cells

While searching for neurons, we continuously applied samples from our stimulus set: G, N, Q, BJ, SC, VO, SO, V100, and V1. We also tested for visual responsiveness (to the sight of food, a saline-associated square plaque, the approach of a taste stimulus toward the mouth, objects, faces, head movement, and lip-smacking) and audi-

tory responsiveness (a 500-Hz tone, coo-calls, grunts, and vocalization), given that stimuli of these types do activate some OFC neurons (Rolls et al. 1996, 2003). When neurons were insensitive to these stimuli, we classified them as nonresponsive. Only cells responding consistently to at least one stimulus of the array were recorded, all stimuli being applied 4 to 6 times in permuted sequences.

RESULTS

The data described in this report were obtained during 99 recording tracks in three hemispheres of two monkeys. Out of 897 screened neurons in the OFC region, 48 neurons (5.4%) responded to fat, viscosity, and/or taste. Visual responses (objects, movement) were clear in 14.3%, and 0.8% showed auditory responses. The remainder of the neurons (78.0%) were unresponsive to the stimuli used. We first show examples of the types of neuron found, and then in Fig. 5 provide a breakdown of the number of each type of neuron found in the form of a Venn diagram.

An example of a fat-responsive neuron is shown in Fig. 1, in a poststimulus time histogram (psth) and rastergram. This neuron showed no statistically significantly different responses to the members of the viscosity series (which includes water, V1) [$F(4,14) = 1.0$, $P = 0.43$], but showed robust and consistent responses to vegetable oil, mineral oil, and silicone oil. The oil responses tended to peak at around 2 s poststimulus delivery for this cell. The responses to the oils calculated over the first 1-s poststimulus period were significantly different from both spontaneous and V10–V100 ($P < 0.001$), allowing us to classify it as a fat-responsive cell.

Figure 2 shows another example of a fat-responsive neuron where the evoked neuronal activity to the indicated stimuli is plotted as a function of viscosity. The cell showed strong and similar responses to all the oils tested, but did not respond to any of the CMC viscosity series below 10,000 cP, and to none of the CMC series with viscosities in the range of the oils. As for the neuron illustrated in Fig. 1, the neuronal responses for the neuron shown in Fig. 2 were significantly different between the oils and the spontaneous firing rate and V10–V100 (both $P < 0.001$). Further, in contrast to the robust excitatory responses to safflower oil (45 ± s/s) and coconut oil (50 ± s/s), which are rich in linoleic and lauric acid bound into triglycerides, the responses to linoleic and lauric acid were slightly

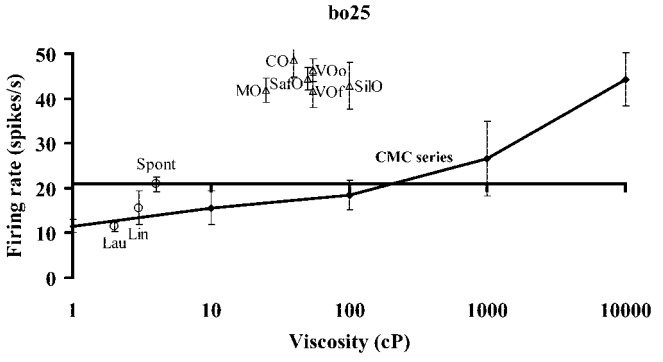

FIG. 2. Evoked activity graphed against apparent stimulus viscosity for fat-responsive neuron bo25. Line indicates responses to CMC series. Mean and SE responses calculated in 1-s period over 4–6 trials are shown here and elsewhere unless otherwise indicated. Oils evoked significantly higher activity than either spontaneous activity or CMC at corresponding apparent viscosities. (For abbreviations used in this and subsequent figures see Table 1.)

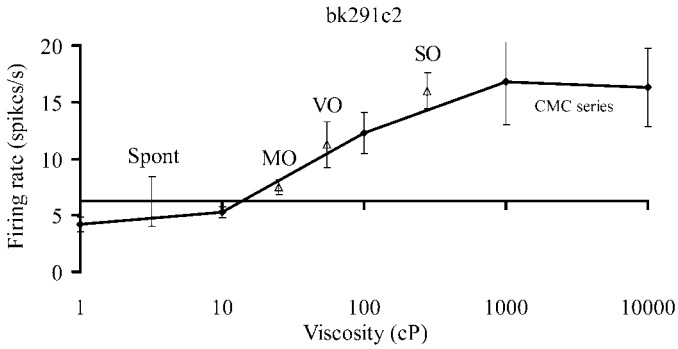

FIG. 3. Evoked activity graphed against apparent stimulus viscosity for viscosity-sensitive neuron bk291c2. Line indicates responses to CMC series. Oil-evoked activity follows that evoked by CMC-viscosity stimuli at corresponding apparent viscosities.

below the spontaneous rate, providing evidence that the neurons did not respond to fats based on gustatory sensitivity to the fatty acids.

In some neurons, the responses to oils were apparently determined by the viscosity of the oils, and the neurons were effectively viscosity-sensitive rather than fat-sensitive. The neuron illustrated in Fig. 3 showed an increasing neuronal response as the viscosity of the CMC series increased from V10 to V1000; and the responses to mineral, vegetable, and silicone oil, plotted at their viscosities, closely follow this viscosity sensitivity curve.

We also observed neurons that did respond to the CMC viscosity series but not to the oils. This type of neuronal response, which also illustrates how neurons can be tuned to a range of viscosities, is exemplified by the neuron shown in Fig. 4. The neuronal responses show an upward trend with increasing viscosity (V1–V1000) and a reduction at V10000. However, none of the oils evoked significant activity. Thus the responses of this neuron show another way in which OFC neurons can discriminate between fat texture and viscosity, by in this case responding to information conveyed through a viscosity information channel but not through a fat-sensitive information channel. Part of the interest of this type of neuron is that, although the oils had viscosities that were in the range 25–100 cP (see Table 1), the neuron did not respond to this level of viscosity when it was expressed through the presence of an oil. This provides evidence that oils must therefore have other texture properties (reflected, e.g., in their slickness) that prevent this type of neuron from responding. This neuron had

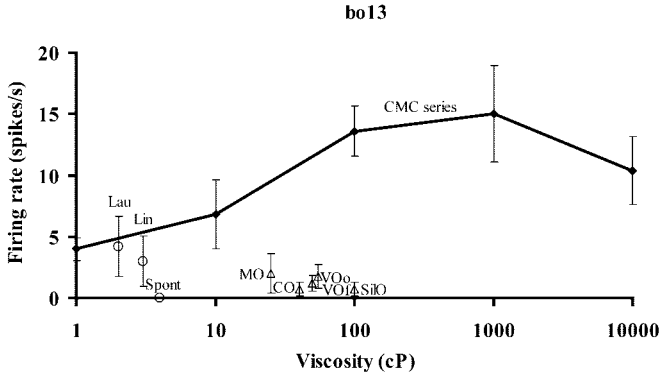

FIG. 4. Evoked activity graphed against apparent stimulus viscosity for neuron bo13. Line indicates responses to CMC series. This neuron did respond to viscosity (of the CMC series) but no activity was evoked by oils.

firing rates to linoleic and lauric acid (4 and 3 spikes/s, respectively) that were predictable by their viscosity, as shown in Fig. 4.

Of the 14 neurons with responses to fat in the mouth where the response to fat was independent of viscosity (i.e., could not be predicted from viscosity) (1.6% of all screened neurons), 9 responded to both taste and to fat, 4 to taste and to viscosity, and one did not respond to taste or to viscosity (see Fig. 5, which is a Venn diagram). Thirteen of the 18 neurons responsive to viscosity also responded to taste, 4 of those also to fat where the response to the fat could not be predicted from the viscosity, and 5 responded only to viscosity. In addition, the number of neurons that were tuned to the CMC viscosity series and that did not respond to fat in the way that would be predicted by the CMC viscosity tuning (see example in Fig. 4) was 4 of the 50 neurons analyzed (not shown in Fig. 5). As shown in Fig. 5, 20 of the 48 neurons were unimodal taste, 5 had unimodal viscosity sensitivity, and the total number of neurons categorized as fat-sensitive was 14.

The average responses across all fat cells that also responded to taste ($n = 13$) and all other taste cells ($n = 29$) are indicated in Fig. 6. None of the responses was significantly different between the groups. Glucose and BJ were clearly the more effective gustatory stimuli. The breadth-of-tuning metric (Smith and Travers 1979) of fat-responsive taste cells to H, Q, N, and G was 0.76 ± 0.07 and of nonfat-responsive taste cells (including viscosity-sensitive taste cells) was 0.77 ± 0.05 ($P = 0.881$). The corresponding sparsenesses are 0.68 ± 0.07 and 0.69 ± 0.04 ($P = 0.914$). Most neurons of either group responded best to G (Fig. 6, *inset*): of fat-responsive taste cells 8 had the best responses to G, 1 to H, 1 to N, 1 to M, 1 to Q, and 1 to multiple stimuli. Of nonfat-responsive taste cells 14 had the best responses to G, 2 to H, 6 to N, 1 to M, 6 to Q, and 0 to multiple stimuli. (The best stimulus for a neuron was the stimulus to which it had the largest difference from the spontaneous firing rate. If the second-best stimulus produced a firing rate within 1 spike/s of that produced by the best stimulus, then that neuron was categorized as having multiple best stimuli.)

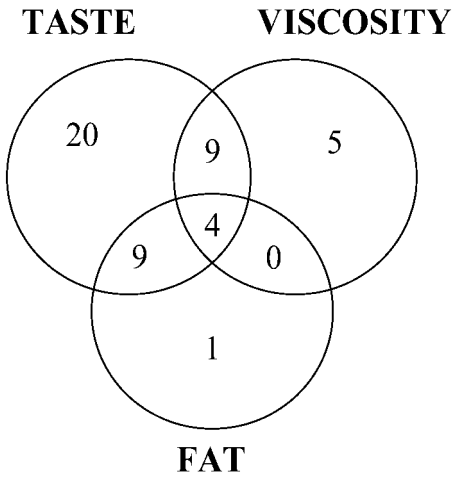

FIG. 5. Venn diagram indicating number of neurons sensitive to each modality as defined in METHODS. Fourteen neurons responding to fat had responses to fat that could not be predicted from their responsiveness to viscosity in CMC viscosity series. Four of these 14 neurons did have some response to some CMC viscosity series stimuli.

The representation of the similarity of the stimuli by the population of neurons was approached with cluster analysis, based on the first 1 s of poststimulus activity, and was performed on the responses of the 48 neurons (with 8 further neurons that responded to other oral stimuli such as temperature) included in the analyses (see Fig. 7). (These 56 neurons were included in all the population analyses so that not only the stimuli included in the experiments described here, but also oral temperature stimuli, could be included in a subsequent comprehensive analysis of the encoding provided by this population of neurons.) The organization of the dendrogram is striking: a clear separation was found between the oils, the tastants (other than H and Q), and the CMC viscosity stimuli. The oils are clustered most closely together ($r > 0.94$) and join with SC at $r = 0.88$, and are next joined at $r = 0.71$ by the cluster consisting of V1–V10000, H, Q, and the ffas. Next the further tastants N and M join at 0.63, and G and BJ are added to the cluster at $r = 0.56$. This segregation between viscosity and oils is also apparent from the multidimensional space (Fig. 8): oils are located closely together, clearly separate from the viscosity series, while being located next to (*x*-axis) and in between (*y*-axis) the tastants. Notably, the oils and the CMC viscosity texture stimuli were located outside the region bounded by the 5 taste stimuli (G, N, H, Q, and M), providing further evidence that fat texture and the viscosity of stimuli are represented by means independent of taste.

To investigate how fat neurons represent the stimulus set, we performed the same analyses based on the 14 statistically identified fat neurons. Figure 9 shows a nearly complete similarity in the response profiles among the oils, given that all oils are clustered at $r > 0.98$. These neurons do not discriminate between the oils based on their very different chemical properties. The oils are joined at $r = 0.96$ by single cream; next at $r = 0.75$ to V1000 and V10000; and only at $r = 0.48$ with the other viscosity stimuli, H, Q, and the ffas. Low correlations are found between this cluster and the tastant clusters of M and N, and G and BJ (range: 0.20–0.27).

Consistent responses by this population of neurons in the OFC to the free fatty acids linoleic acid (LiA) and lauric acid (LaA) were not found; that is, for most neurons the activity evoked by these stimuli was indistinguishable from that evoked by water. In particular, of 37 neurons tested with lauric and linoleic acids, 34 had no significant responses compared with that of water. Of the three neurons that had statistically significant responses in this comparison, all three consisted of a smaller response than was obtained with water, and in two cases the statistical significance was marginal (i.e., $P \approx 0.05$). To assess whether the firing rates obtained for lauric and linoleic acids could predict the responses of the neurons to coconut oil (high in lauric acid conjugated to glycerol) and to safflower (high in linoleic acid conjugated to glycerol), linear regression analysis was performed across the 14 fat-sensitive neurons. There was no significant correlation between the responses to the fatty acids and these two fat stimuli. (For lauric acid, $r = 0.45$, $P = .20$; for linoleic, $r = 0.61$, $P = 0.06$; and by contrast for silicone oil vs. coconut oil, $r = 0.99$, $P < 0.001$, whereas for silicone oil vs. safflower oil, $r = 0.99$, $P < 0.001$.) Thus the responses to fats by this population of neurons cannot be accounted for by sensitivity to lauric acid and linoleic acid. The difference in the neural representation between the oils and ffa is indicated in Fig. 10. The ffa LiA and LaA are

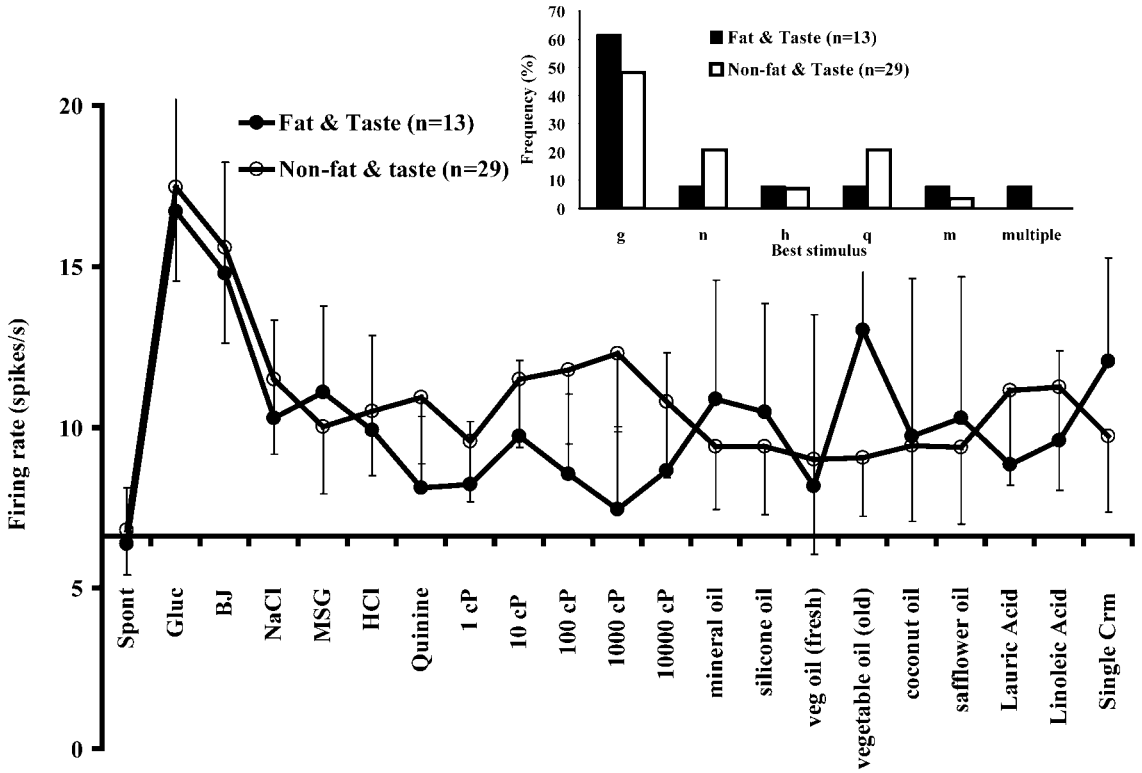

FIG. 6. Responses to all stimuli in stimulus-array averaged across all neurons that were either taste and fat sensitive ($n = 13$), or taste and any stimulus apart from fat ($n = 29$). No significant differences were found between groups for any stimulus. *Inset*: percentage of each group of neurons responding best to indicated tastants.

located more closely to V1 (water) and V10 than to the oils. A clear organization exists among the tastants (5 leftmost stimuli), CMC viscosity series (located in order of viscosity), and the oils (a relatively separate, tight group).

Localization of recordings

The reconstructed positions of the neurons in this study are shown in Fig. 11. The uni- or multimodal responses of the neurons are indicated by numbers. Fat- and viscosity-sensitive neurons are located in the caudolateral aspect of the OFC, in a similar region to gustatory neurons. The regions within which recordings were made are delimited by arrows.

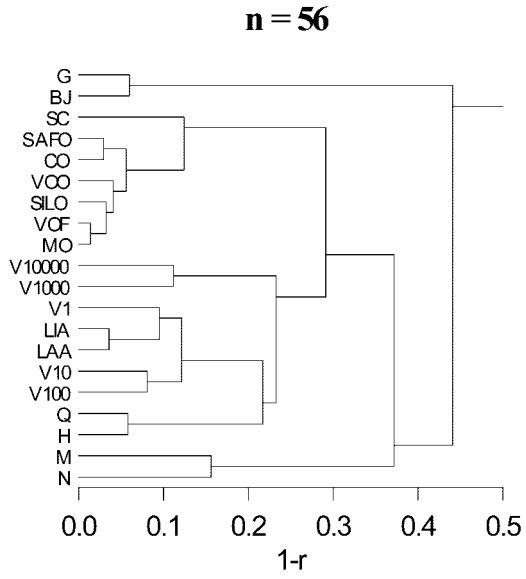

FIG. 7. Stimulus dendrogram based on 56 orally responsive neurons. (1 − r) is measure of dissimilarity of clusters, where r is correlation coefficient.

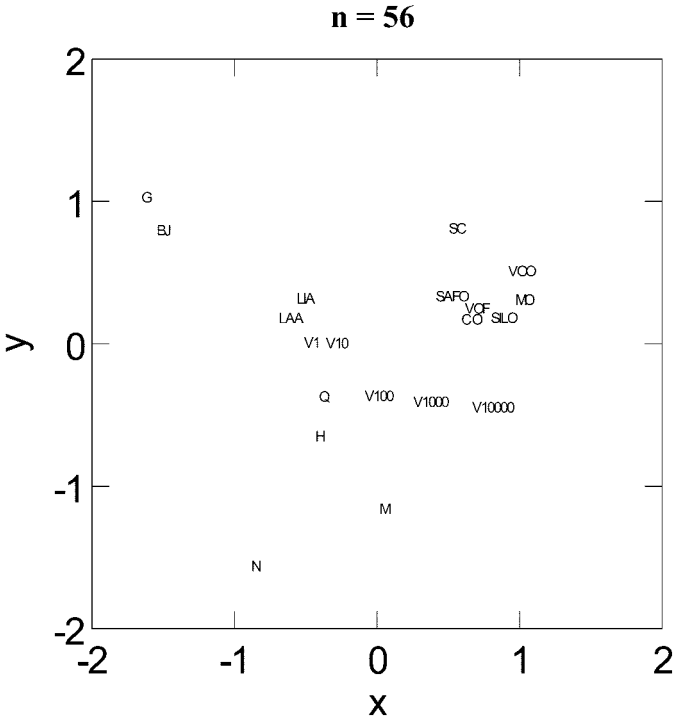

FIG. 8. Stimulus space (multidimensional scaling) of stimulus similarity based on across-neuron response profiles of 56 neurons.

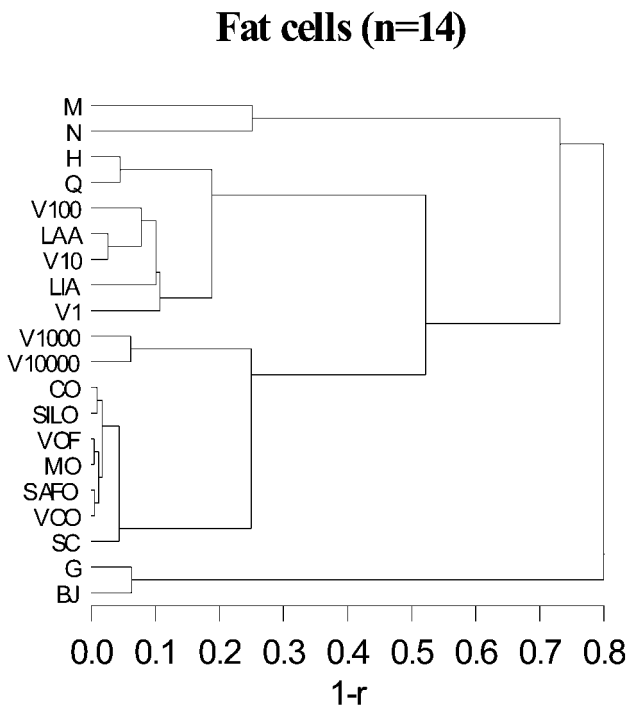

FIG. 9. Stimulus dendrogram based on 14 fat-responsive neurons.

DISCUSSION

The results described in this report extend the discovery of oral fat-sensitive neurons in the primate OFC (Rolls et al. 1999). First, the present results confirm that fat-sensitive neurons respond not only to fats such as cream and vegetable oil, but also to chemically different substances that have a similar slick or oily texture such as mineral oil (pure hydrocarbon) and silicone oil [$(Si(CH_3)_2O)_n$]. This evidence thus indicates that the mechanisms that sense fat and to which these neurons respond are sensing a physical rather than a chemical property of the stimuli. Second, the results provide evidence for the first time that the responses of fat-sensitive neurons are not based on a texture information channel that is tuned to viscosity. In particular, although some neurons in the OFC are tuned to viscosity (see examples in Figs. 3 and 4, and the Venn diagram in Fig. 5), many (10/14) of the fat-sensitive neurons did not respond at all to the viscosity series of stimuli (see example in Fig. 2) or had responses to the fats and some of the CMC viscosity series, where the response to fat could not be accounted for by viscosity (4/14); and 4 neurons were responsive to viscosity but did not respond to fat (see example in Fig. 4). The latter type of neuron (Fig. 4) is rather interesting because the implication is that, although there is a viscosity-sensing channel that responds to stimuli including fats based on their viscosity (Fig. 2), there is also a mechanism for representing viscosity when it is not produced by a fatty oily stimulus, as in Fig. 4.

There are important conclusions then about the representation of oral texture in the brain (and illustrated by the types of neuron shown in Figs. 2–4). *1*) There is an information channel that represents fat independently of viscosity. *2*) There is an information channel that represents viscosity and also responds to fat based on the viscosity of the fat. This channel thus responds to viscosity independently of whether the eliciting stimulus is a nonfat or a fat. *3*) There is an information channel that encodes viscosity, provided that it is not associated with an oily substance such as a fat. The third type of channel could reflect a separate sensing mechanism in the mouth, or it could reflect competitive and expansion recoding processes (see Rolls and Deco 2002; Rolls and Treves 1998) produced in the cortex by inputs reflecting, for example, fat sensitivity without viscosity in a first channel and another channel viscosity with fat sensitivity in another channel. Third, the results provide evidence not only that fats are detected by a somatosensory texture channel, but also that (at least in nonhuman primates) fat-sensitive neurons are not generally or strongly activated by chemical stimuli such as the free fatty acids linoleic acid and lauric acid, which might activate gustatory receptors. Further, the responses of the neurons we describe to fatty acids do not predict the responses of the neurons to fat. [This is in contrast to the responses to silicone oil, which very strongly ($r = 0.99$) and significantly ($P < 0.001$) predict the responses of the neurons to fatty oils.] Some of these issues are elaborated on below.

The neurons in the OFC that respond to the texture of fat independently of the fat's viscosity and chemical composition represent 1.6% of all screened OFC neurons. However, quite a large area of the OFC was screened (see Fig. 11), and the actual proportion may be higher within localized subregions of the OFC, given the tendency for cortical neurons to cluster according to the effective stimuli (Rolls and Deco 2002). [This impression is similar to that obtained when recording in the inferior temporal visual cortex, in which local clusters of neurons with responsiveness to the same general types of visual stimuli are often found (Rolls 2000; Wang et al. 1998).] This local clustering may be attributed to local topographic map formation in a high-dimensional stimulus space, as described by Rolls and Deco (2002). Despite high efficiency in obtaining orally responsive neurons in such clusters in the OFC, we moved to other areas to maintain tissue integrity and

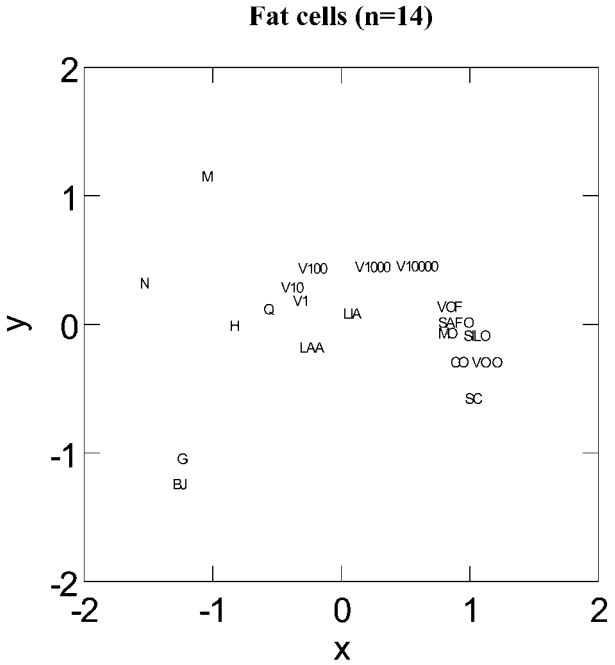

FIG. 10. Stimulus space (multidimensional scaling) of stimulus similarity based on across-neuron response profiles of 14 fat-responding neurons.

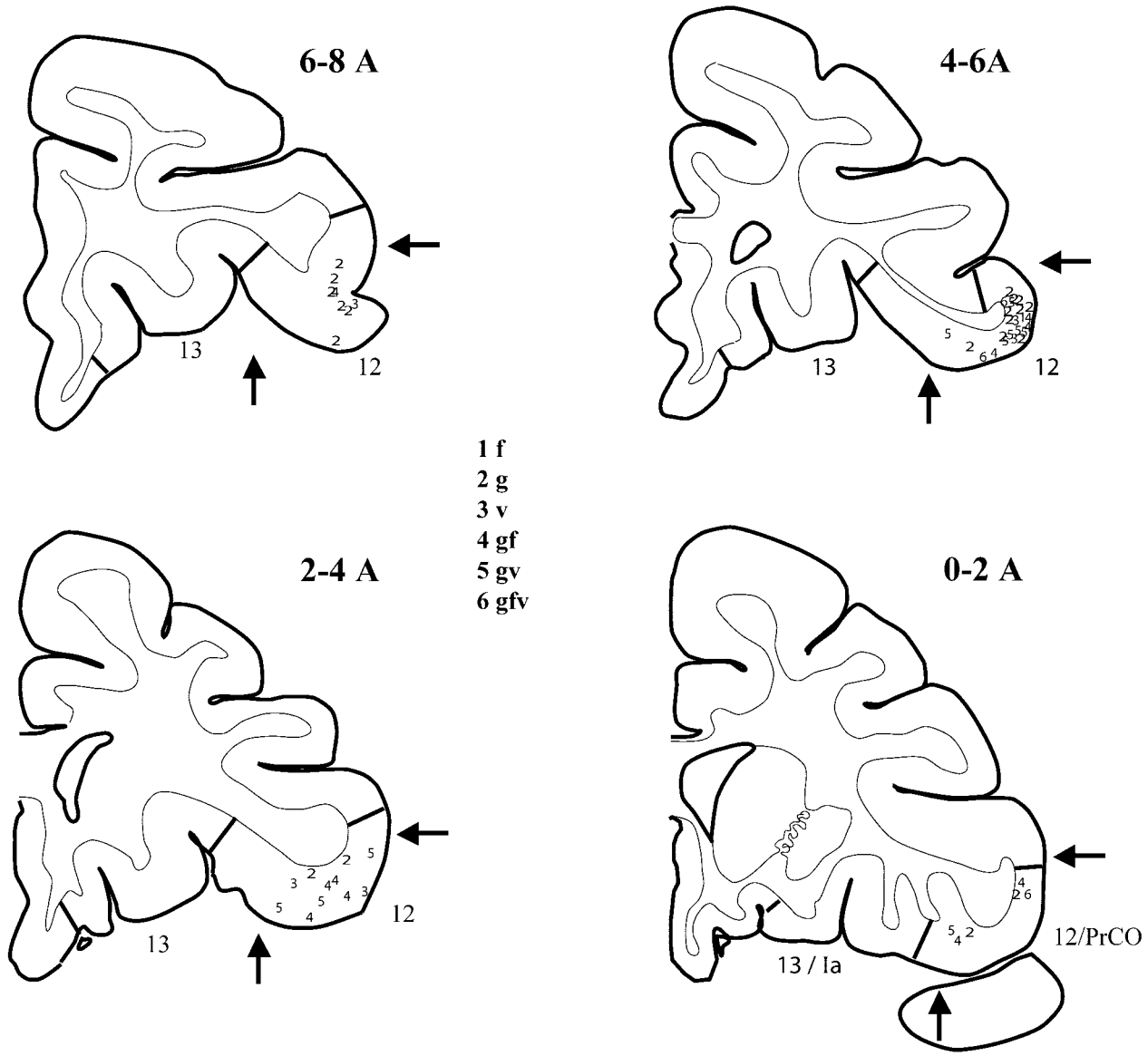

FIG. 11. Reconstructed positions of neurons. Number with which location of each neuron is indicated shows whether neuron was tuned to f (fat), g (taste), v (viscosity), or to combinations of these. Neurons were located within orbitofrontal cortical area. (For one macaque reconstructions are based on histology and X-ray data for every track, and for the other on X-ray data for every track and standard atlas calibrated in X-ray coordinates.) *6–8 A*: coronal section was taken 6–8 mm anterior to sphenoid process used as a landmark (Aggleton and Passingham 1981), at approximately the A-P level of optic chiasm. Arrows show region within which neurons were recorded. Approximate boundaries of architectonic areas according to Carmichael and Price (1994) are shown: 12, 13: areas of orbitofrontal cortex; 13/Ia: transition region between area 13 and area with cytoarchitectonic characteristics, designated as agranular insula; 12/PrCO: transition region between area 12 and area with cytoarchitectonic characteristics, designated as precentral opercular cortex.

sample a large area of the OFC. We note that the proportions of many different classes of neuron in the primate OFC are low (Rolls and Baylis 1994; Rolls et al. 2003), but that nevertheless these neurons appear to be performing important functions that are validated by the effects found when these areas have lesions in humans (Hornak et al. 1996, 2003a,b; Rolls et al. 1994).

The main finding that fat representations of the texture of oral fat can be independent of viscosity raises the issue of what other physical properties the fat-sensitive neurons are responding to. To test this, we measured the correlation between the responses of the neurons described here and the coefficient of sliding friction (Halling 1976). The coefficient was calculated using the responses of each fat-sensitive neuron to the viscosity series and the oils, and for no neuron was a significant correlation found. (The absolute value of the correlations was 0.34, SD 0.18.) Another possibility is that the lipophilicity or partition coefficient (Leo et al. 1971) of the stimuli may be important because the oils are all lipophilic, in contrast to all other water-soluble stimuli. This property may underlie some idiosyncratic behavior in the mouth, for example, oral coating and thin-film rheological properties. Another possibility is that the interaction of the oils with saliva may be a determining factor in the responsiveness of the fat-sensitive neurons. The oils form droplets in saliva, and thus the degree of emulsification may be important.

The common perceptual quality among the oils is the slick/fatty mouth feel. The function of the neurons described here may be to allow recognition of fatty substances in the mouth, based on texture information received through the somatosensory system. Consistent with this, Mela (1988) reported that humans rate the fat content of dairy products based on their textural properties. We note that the types of neuron described here, responding to fat independently of viscosity, to viscosity whether it is produced by nonfat or by fat, and to viscosity when it is not being produced by a fatty/oily texture, provide an excellent representation of many textural properties of food, including creaminess, for which ratings provided by humans depend on a variety of textural properties (Bourne 2002). Further breadth to the representation is provided by the taste inputs to some of the neurons described here and by Rolls et al. (1999), and by the odor inputs to, for example, some fat-sensitive neurons (Rolls et al. 1999). This is consistent with the hypothesis that a food's flavor (and appearance) is represented in the OFC by integration of somatosensory, gustatory, and olfactory information in such multimodal neurons (cf. Rolls and Baylis 1994). It would be of great interest to identify the interactions between such modalities in multimodal neurons. In particular, the interactions between viscosity and fat (Mela 1988) and between sweet stimuli and fat (Drewnowski 1987) may be important for understanding human perceptual and hedonic behavior. We note that there is evidence, from just a few neurons so far, that OFC neurons responsive to fat may indeed represent the hedonic aspects of fat in the mouth, in that the few neurons tested decrease their responses to fat when this is fed to satiety (Rolls et al. 1999). Because oral fat can be sensed as fatty even when we are satiated, it could be that there is a representation of fat texture in a cortical area such as the primary taste cortex where taste responses are independent of hunger, a topic that will be useful to investigate further.

As reported before (Rolls et al. 1999), fat-responding neurons are not necessarily also taste sensitive, although in our sample, 13 of the 14 fat-sensitive neurons had taste responses (see Fig. 5). Furthermore, if gustatory mechanisms induced by fatty acids were critically involved in fat sensing, then neurons responding to safflower oil should have responded to its main fatty acid, linoleic acid, and correspondingly for coconut oil and lauric acid. Not only were few responses obtained to these fatty acids, but also the responses of the fat-sensitive neurons were not correlated with their responses to these fatty acids, and indeed in the stimulus spaces (Figs. 8 and 10) no such association was evident. Together, these points of evidence suggest that fat in the mouth can be sensed in primates at least independently of any oral gustatory mechanism for free fatty acids (a mechanism suggested by Gilbertson 1998). These data may suggest that different sensing mechanisms and percepts are evoked by ffa as compared with fatty oils. Perceptual responses to ffa, if large enough not to also taste sour (Forss 1972), depend at least partly on the trigeminal-nociceptive pathway and may be associated with the percept of oral irritation. The oils, triglyceride-based or not, are sensed by a somatosensory-textural pathway and may be associated with the mouth feel of fatty/slickness.

In conclusion, the data presented in this study show that OFC neurons can be specifically tuned to oral fats, and that fat can be represented independently of a viscosity-sensitive texture channel. Further, the results show that viscosity can be represented independently of fat texture. In addition, although both fat texture and viscosity can be represented independently, other neurons respond to combinations of fat and/or viscosity and/or taste inputs, thereby providing a rich representation of the sensory properties of food in the mouth, in which particular combinations of the above-noted properties can be represented separately from the components. This allows for subjective and behavioral responses that can be based on particular combinations of these inputs, providing for great sensory capability in choosing and learning about particular complex foods. This provides the required computational basis both for sensory-specific satiety, which can then be computed by making it a property of the combination-sensitive neurons in the orbitofrontal cortex in that they habituate over the course of a meal; and for learning associations between the complex sensory properties of a food and its nutritional consequences, which do not overgeneralize to other similar foods or the components from which the food complex is formed (see Rolls 1999; Rolls and Deco 2002; Rolls et al. 1989).

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DISCLOSURES

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